Claims 1-3, 5-28, 31-36, 70-72, 74-77, 79 and 80 are pending in the application. Claims 4, 29, 30, 37-69, 73, 78 and 81 have been withdrawn from consideration by the Examiner as being non-elected. Claim 7 was canceled, without prejudice to filing one or more related applications directed to the canceled subject matter thereof.

At pages 2-5 of the Office Action, claims 1-3, 5-28, 31-36, 70-72, 74-77, 79 and 80 have been rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,846,966 ("Rosenblum et al.") in view of U.S. Patent No. 5,300,288 ("Albright"), U.S Patent No. 4, 837,255 ("Dechow") and U.S. Patent No. 5,661,145 ("Davis").

It is asserted that Rosenblum et al. teach the instant cholesterol absorption inhibitors, their application for lowering serum cholesterol and combination with other cholesterol lowering agents such as simvastatin. Office Action at page 2. Further, it is asserted that Rosenblum et al, teach a daily dosage in a range of 5 mg to 1000 mg a dose given 1 or two times a day and that the exact dose would depend upon various conditions. Office Action at page 2.

It is acknowledged that Rosenblum et al. do not teach a combination of a hydroxyl substituted azetidinone, such as ezetimibe, and a bile acid sequestrant, e.g., cholestyramine, further with a cholesterol biosynthesis inhibitor, e.g. simvastatin. Office Action at page 2.

It is alleged that Albright discloses that cholestyramine is an old and well-known cholesterol lowering agent and that Dechow teaches a method of lowering cholesterol by administering cholestyramine. Office Action at pages 2-3.

It is alleged that it would have been obvious to one of ordinary skill in the art, at the time that the claimed invention was made, to make a cholesterol lowering composition comprising hydroxyl substituted azetidinone, e.g., ezetimibe, and the well known cholesterol lowering agent cholestyramine, citing *In re Kerkoven*, 205 U.S.P.Q. 1069. Office Action at page 3.

It is further alleged that optimization of a result-effective parameter, e.g., effective amount of a therapeutic agent, is within the skill of the artisan, citing In re Boesch and Slaney, 204 U.S.P.Q. 215, and that the specific amount of 10 mg is within the range disclosed by Rosenblum et al..

Applicants respectfully traverse this rejection and request that the rejection be reconsidered and withdrawn.

The law is replete with cases holding that there must be some suggestion or motivation in the prior art to combine the references. When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992).

The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d at 1784; In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

"It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious....'[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" In re Fritch, 23 U.S.P.Q.2d at 1784 (quoting In re Fine, 5 U.S.P.Q.2d at 1600).

"The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence." Manual of Patent Examining Procedure, (Rev. 1, Feb. 2003) § 716.01(d) and In re Oetiker, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

None of the cited references, taken alone or in combination as proposed in the final Office Action, suggests or discloses administering a combination of at least one bile acid sequestrant and about 10 milligrams of sterol absorption inhibitor of Formula (I) (such as ezetimibe).

It is respectfully submitted that the combination of the references cited by the Examiner as rendering the claimed invention obvious is improper because there is no suggestion in the cited references to combine the claimed components of about 10 milligrams of sterol absorption inhibitor (such as ezetimibe) and cholestyramine.

In the In re Kerkoven case cited by the Examiner, the Court found the motivation or suggestion to combine two materials each disclosed in a separate reference from the fact that each reference taught the individual materials for the very same purpose as in the claimed combination. That is not the situation here.

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. See ZETIA™ (ezetimibe) Tablets Package Insert at column 1 (Merck/Schering-Plough Pharmaceuticals) (October 2002) included in the Information Disclosure Statement filed January 15, 2004.

The cholesterol content of the liver is derived predominantly from three sources. Id. The liver can synthesize cholesterol, take up cholesterol from the blood from circulating lipoproteins, or take up cholesterol absorbed by the small intestine. Id. Intestinal cholesterol is derived primarily from cholesterol secreted in the bile and from dietary cholesterol. Id.

Ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-reducing compounds (HMG CoA reductase

inhibitors, bile acid sequestrants (resins), fibric acid derivatives, and plant stanols). Id.

Ezetimibe does not inhibit cholesterol synthesis in the liver (like HMG CoA reductase inhibitors), or increase bile acid excretion (like bile acid sequestrants). Id. Instead, ezetimibe localizes and appears to act at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. Id. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of HMG CoA reductase inhibitors. Id.

Ezetimibe does not operate by the same mechanism as either cholestyramine or cholesterol biosynthesis inhibitors. Because of the difference of the way that each component of the presently claimed combination acts, it is respectfully submitted that the rejection is based upon an improper combination of references. There is no suggestion or motivation in the references to combine the claimed components that operate by these different mechanisms.

It is impermissible to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *No motivation has been provided to select these two particular types of lipid management compounds out of numerous lipid management compounds.*

Further, *there is no motivation to select the claimed amount of about 10 milligrams* of sterol absorption inhibitor (such as ezetimibe). In re Boesch and Slaney relates to a nickel based alloy composition, not administration of a therapeutic agent to a human that is less predictable.

Accordingly, reconsideration and withdrawal of the §103(a) rejection is respectfully requested.

Applicants respectfully request that the Examiner return an initialed PTO-1449 form for each of the Information Disclosure Statements submitted on August 21, 2002 (EFS Nos. 17231 and 17260), April 4, 2003 and April 12, 2004 indicating that the Examiner has considered each of the references cited therein.

In view of the foregoing remarks, it is respectfully submitted that all of the pending claims in the present application are distinguishable from the cited prior art. Accordingly, reconsideration and withdrawal of the rejection and an early Notice of Allowance are respectfully requested.

Respectfully submitted,

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Ann Marie Cannoni
Registration No. 35,972
WEBB ZIESENHEIM LOGSDON ORKIN & HANSON, P.C.
700 Koppers Building
436 Seventh Avenue
Pittsburgh, PA 15219
Phone: (412) 471-8815
Fax: (412) 471-4094
E-mail: acannoni@webblaw.com